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ORIGINAL REPORT

Neoadjuvant Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin With Pegfilgrastim Support in Muscle-Invasive Urothelial Cancer: Pathologic, Radiologic, and Biomarker Correlates

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See accompanying editorial on page 1868 and article on page 1895

A B S T R A C T

Purpose
In advanced urothelial cancer, treatment with dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) results in a high response rate, less toxicity, and few dosing delays. We explored the efficacy and safety of neoadjuvant ddMVAC with pegfilgrastim support in muscle-invasive urothelial cancer (MIUC).

Patients and Methods
Patients with cT2-cT4, N0-1, M0 MIUC were enrolled. Four cycles of ddMVAC were administered, followed by radical cystectomy. The primary end point was pathologic response (PaR) defined by pathologic downstaging to ≤ pT1N0M0. The study used Simon's optimal two-stage design to evaluate null and alternative hypotheses of PaR rate of 35% versus 55%. Secondary end points included toxicity, disease-free survival (DFS), radiologic response (RaR), and biomarker correlates, including ERCC1.

Results
Between December 2008 and April 2012, 39 patients (cT2N0, 33%; cT3N0, 18%; cT4N0, 3%; cT2-4N1, 43%; unspecified, 3%) were enrolled. Median follow-up was 2 years. Overall, 49% (80% CI, 38 to 61) achieved PaR of ≤ pT1N0M0, and we concluded this regimen was effective. High-grade (grade ≥ 3) toxicities were observed in 10% of patients, with no neutropenic fevers or treatment-related death. One-year DFS was 89% versus 67% for patients who achieved PaR compared with those who did not (hazard ratio [HR], 2.6; 95% CI, 0.8 to 8.1; $P = .08$) and 86% versus 62% for patients who achieved RaR compared with those who did not (HR, 4.1; 95% CI, 1.3 to 12.5; $P = .009$). We found no association between serum tumor markers or ERCC1 expression with response or survival.

Conclusion
In patients with MIUC, neoadjuvant ddMVAC was well tolerated and resulted in significant pathologic and radiologic downstaging.

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INTRODUCTION

Neoadjuvant chemotherapy has been established as a standard treatment for muscle-invasive urothelial cancer (MIUC). Two phase III studies have demonstrated an increase in overall survival (OS) for patients who underwent chemotherapy before cystectomy compared with cystectomy alone.[1,2] A meta-analysis of 3,005 patients from 11 clinical trials revealed a 14% decreased risk of death and 5% absolute increase in OS among patients who received neoadjuvant chemotherapy.[3]

The 4-week chemotherapy regimen MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) was first developed in the 1980s. It has since been considered one of the most active chemotherapy regimens for UC.[4] In 1992, a randomized multicenter study of 239 patients demonstrated a median survival of 13.5 months in patients with UC treated with MVAC compared with 8.2 months in patients treated with single-agent cisplatin ($P = .04$).[5] In the neoadjuvant setting, a North American US Intergroup study showed a significant survival advantage in patients treated with neoadjuvant

MVAC chemotherapy. Most importantly, pathologic downstaging of the primary tumor was associated with improved outcome.[1,6]

However, the 4-week so-called traditional MVAC regimen without granulocyte colony-stimulating factor (G-CSF) support is associated with significant toxicity, which often leads to treatment interruption, delays, and early termination, thus compromising benefit. In the US Intergroup study, 108 (72%) of 150 patients experienced grade ≥ 3 toxicities. As a result, dose-dense MVAC (ddMVAC), originally called high-dose MVAC, was developed to improve on the MVAC regimen by attempting to reduce toxicity and improve treatment benefit. The ddMVAC regimen is administered on a shortened 2 weeks–per–cycle schedule with double the dose-intensity of cisplatin and doxorubicin, while reducing the dose of methotrexate and vinblastine by one third. Each cycle is supported by the administration of G-CSF. One study comparing ddMVAC with traditional MVAC in patients with metastatic disease showed an improvement in complete response rate from 11% to 25% ($P = .006$) and an increased probability of 5-year OS from 13.5% to 21.8% ($P = .04$), despite a similar median OS. The rates of neutropenic fever as well as grades 3 and 4 hematologic and GI toxicities were significantly reduced in the ddMVAC regimen with G-CSF support, and no worsening renal function was reported.[7]

On the basis of the findings from these studies, we designed a phase II multicenter study to examine the safety and efficacy of neoadjuvant ddMVAC with pegfilgrastim (pegylated G-CSF) support in patients with MIUC. Treatment efficacy was defined by pathologic response (PaR) and radiologic response (RaR). Associations between response and longer-term clinical outcomes as well as potential biomarkers were also assessed.

PATIENTS AND METHODS

Eligibility

Eligible patients were required to have evidence of MIUC in a pretreatment transurethral biopsy sample. Patients with all histologic subtypes were eligible if urothelial carcinoma was the predominant feature. Patients with any elements of small-cell carcinoma were excluded. Patients with clinical stage T2-T4a and ≤ N1 disease (single lymph node ≤ 2 cm in greatest dimension) on imaging were eligible (American Joint Commission on Cancer, sixth edition). Patients were required to have adequate kidney (creatinine clearance by Cockcroft-Gault formula > 50 mL/min), bone marrow, and liver functions. This clinical trial was approved by the institutional review boards at all four participating institutions and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.[8] All patients provided written consent before participation.

Study Design and Treatment Plan

This was an investigator-initiated, multicenter, open-label phase II study, where enrollment was monitored and managed by the office of Quality Assurance for Clinical Trials at the Dana-Farber Cancer Institute. Eligible patients underwent four cycles of ddMVAC chemotherapy in the neoadjuvant setting, as summarized in Table 1. All patients received pegfilgrastim approximately 24 hours after the last dose of chemotherapy during each treatment cycle. Radical cystectomy took place between 4 and 10 weeks after chemotherapy completion. During the follow-up period, patients were assessed for disease recurrence and OS. Follow-up schedule with visits and imaging occurred every 3 months for 2 years, followed by every 6 months for 3 years and annually thereafter.

Clinical Assessment

Before registration, collection of detailed medical history, physical examination, baseline ECG, and radiologic disease assessment were performed. Physical examination was performed and Eastern Cooperative Oncology Group performance status, vital signs, and blood tests (complete blood count, serum chemistry tests, and serum tumor markers previously described to be associated with urothelial cancer [cancer antigen 19-9 (CA19-9), CA125, and beta–human chorionic gonadotropin (HCG)]) were recorded on the first day of each treatment cycle. Tumor tissue from pretreatment biopsies was collected. Toxicity was assessed before each treatment and monitored throughout the treatment cycle. Toxicities were documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Table 1. Treatment Administration Schedule: Dose-Dense MVAC (every 14 days for four cycles)

Agent	Dose	Route	Day 1	Day 2	Day 3
Methotrexate	30 mg/m^2	IV	X		
Doxorubicin	30 mg/m^2	IV		X	
Vinblastine	3 mg/m^2	IV		X	
Cisplatin	70 mg/m^2	IV		X	
Pegfilgrastim	6 mg	SC			X

Abbreviations: IV, intravenous; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; SC, subcutaneous.

Radiologic Assessment

Radiologic assessment (imaging of chest, abdomen, and pelvis) was completed at baseline and after chemotherapy completion. Contrast-enhanced magnetic resonance imaging (MRI) was the primary imaging modality for the abdomen and pelvis. Computed tomography scan was used in patients with contraindication to MRI such as indwelling non-MRI compatible medical device or severe claustrophobia. RaR was determined based on a consensus reading by three oncoradiologists. RaR was defined by Schrier et al,[9] where a patient was considered a responder if the bladder tumor had a > 50% decrease in the product of the longest perpendicular diameters and delayed enhancement of residual tumor, and a nonresponder if this was not the case.[10] Patients with enlarged lymph nodes at baseline were considered responders if, in addition to response in the primary bladder tumor, they also demonstrated normalization of node size and delayed enhancement of the nodes.

Biomarker Analysis

Immunohistochemical (IHC) staining of ERCC1 protein expression was performed on formalin-fixed, paraffin-embedded pretreatment tumors specimens. ERCC1 was detected using FL-297 polyclonal antibodies (sc-10785; Santa Cruz Biotechnology, Santa Cruz, CA). Semiquantitative assessment of ERCC1 staining was performed by a single pathologist (S.S.) blinded to the clinicopathologic variables. Each specimen was scored based on the staining intensity and percentage of positive cells. The percentage of positive nuclei was then converted to a proportion score (0, 0%; 0.1, 1% to 9%; 0.5, 10% to 49%; 1.0, ≥ 50%) based on methods described in previous work.[11] An IHC score (H score) was calculated by multiplying the proportion score by the staining intensity, which was graded on a scale of 0 to 3, with 3 indicating the highest intensity. ERCC1 positivity was defined as an H score > 0.1.

Statistical Analyses

The primary end point was PaR, defined as the absence of residual muscle-invasive cancer in the surgical specimen (pathologic downstaging to ≤ pT1pN0), which included pT0, pT1, pTa, and pTis. This study used a Simon's optimal two-stage design to allow for early termination of the trial if there was strong evidence that ddMVAC was not different from standard MVAC therapy. Assuming an ineligibility rate of 5%, the target accrual was set for 39 patients. In the first stage, 18 patients were to be evaluated, and if ≥ seven achieved PaR, 21 additional patients would be enrolled. In total, if PaR was seen in ≥ 17 of 37 eligible patients, the treatment would be declared effective. Per design, there was a 62% chance of stopping enrollment early with a true PaR rate of 35% and 8% chance of stopping early if the true rate was 55%. The design had a power of 85%, assuming one-sided type I error of 0.10. The decision rule was adjusted but operating characteristics maintained for final

Table 2. Baseline Patient Demographic and Clinical Characteristics (N = 39)

Characteristic	No.	%
Age < 65 years	27	69
Male sex	28	72
White race	39	100
Presence of carcinoma in situ	9	23
ECOG PS of 0	36	92
TCC site		
Bladder	36	92
Urothelial, other	3	8
Clinical TNM stage		
T2N0	13	33
T3N0	7	18
T4N0	1	3
T2-4N1	17	43
T2N1	3	7
T3N1	9	23
T4N1	5	13
Unspecified	1	3
Stage		
II	13	33
III	7	18
IV	18	46
Unspecified	1	3

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; TCC, transitional cell carcinoma.

enrollment of 39 eligible patients, such that if 18 of 39 patients achieved PaR, the treatment would be declared effective. A two-sided 80% CI was estimated considering the two-stage design based on Atkinson and Brown methods.[12] Secondary end points included the rate of neutropenic fever and other treatment- and surgery-related toxicities, RaR, and disease-free survival (DFS) and its association with PaR, RaR, and biomarkers.

DFS was defined as time from cystectomy to disease recurrence or death resulting from disease. Patients alive without disease progression at the time of analysis were censored at the date of last disease assessment. Exact binomial rates were calculated with 95% CIs. Association between categorical variables was assessed using Fisher's exact test. DFS was estimated using the Kaplan-Meier method, and distributions within subgroups were compared using the log-rank test. *P* values of ≤ .05 were considered statistically significant.

RESULTS

Patient Characteristics

Thirty-nine patients were enrolled between December 2008 and April 2012. In this cohort, 92% had a primary tumor in the bladder, 72% were men, and 23% had carcinoma in situ present at baseline. Clinical staging distribution is listed in Table 2.

Primary End Point Analysis

Overall, 19 (49%) of 39 patients (two-sided 80% CI, 38 to 61) achieved PaR on cystectomy (Table 3). The observed results allowed rejection of the null hypothesis that PaR was ≤ 35% and implied the data were more consistent with the alternative hypothesis of a PaR rate ≥ 55%. Among the pathologic responders, 10 patients (26%; 80% CI, 17 to 37) achieved complete PaR (pT0). In addition, 14 (82%) of 17 patients with cN1 disease on imaging had pN0 at surgery; no patients with cN0 disease were found to be pN positive. One patient experienced distant metastatic disease after completing four cycles of ddMVAC chemotherapy and did not undergo surgery. The median time to surgery was 6 weeks (range, 4 to 12 weeks) after the last dose of chemotherapy. The median time to surgery was shorter than those reported in prior studies, such as the study by Weight et al.[13]

Table 3. PaR and RaR to Neoadjuvant ddMVAC Chemotherapy

	Bladder (n = 36)		Urothelial, Other (n = 3)		Total (N = 39)		
Response	No.	%	No.	%	No.	%	Two-Sided 80% CI
PaR ≤ pT1	17	47	2	67	19	49	38 to 61
pT0 PaR	10	28	0	0	10	26	17 to 37
RaR	24	67	0	0	24	62	50 to 72

Abbreviations: ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; PaR, pathologic response; RaR, radiologic response.

Secondary End Point Analysis

Treatment exposure and toxicities. Overall, 37 (95%) of 39 patients completed all four cycles of chemotherapy. Two patients discontinued treatment after three cycles because of toxicity. High-grade (grade ≥ 3) chemotherapy-related toxicities were observed in four patients (10%; 90% CI, 4 to 22). These consisted of hand-foot-skin reaction, mucositis, hypokalemia, and neutropenia. No febrile neutropenia or treatment-related deaths were reported. Seven patients had postoperative surgical complications, among which four (11%; 90% CI, 4 to 22) were deemed possibly related to chemotherapy (small bowel obstruction, stoma leakage, elevated creatinine, and infection).

RaR. RaR was observed in 24 (62%) of 39 patients (80% CI, 50 to 72; Table 3). Twelve patients (30%) did not reach RaR, and three patients (8%) were not evaluable. As an example, Gadolinium-enhanced MRI of a radiologic responder versus nonresponder are shown in Figure 1. Of those patients who achieved RaR, 63% also achieved PaR, compared with 27% of patients without RaR ($P = .048$).

DFS and its correlation with PaR and RaR. At the time of this analysis, the median follow-up among survivors was 24 months from registration. Eight patients died as a result of disease progression. Patients who achieved PaR had a 1-year DFS of 89% (95% CI, 61 to 97) compared with 67% (95% CI, 40 to 83) for those patients who did not achieve PaR (hazard ratio, 2.6; 95% CI, 0.8 to 8.1; $P = .08$; Fig 2). Patients who achieved RaR had a 1-year DFS of 86% (95% CI, 63 to 95) compared with 62% (95% CI, 31 to 82) for those patients who did not achieve RaR (hazard ratio, 4.1; 95% CI, 1.3 to 12.5; $P = .009$; Fig 3).

Serum tumor marker analysis. Overall, 10 of 39 patients had at least one elevated serum tumor marker (CA19-9, CA125, or beta-HCG) at baseline. Only two of these 10 patients exhibited normalization of serum tumor markers after chemotherapy, but neither achieved PaR or RaR.

IHC analysis. Of the 39 patients enrolled, 31 had adequate pretreatment tumor biopsy specimens for ERCC1 staining. This subgroup was similar in baseline characteristics to the overall cohort. Twelve patients (39%) were ERCC1 positive. An association between ERCC1 positivity and PaR or DFS could not be detected, with the caveat of the small sample size, which considerably limited power. In our study, 43% of ERCC1-positive patients and 60% of ERCC1-negative patients achieved PaR.

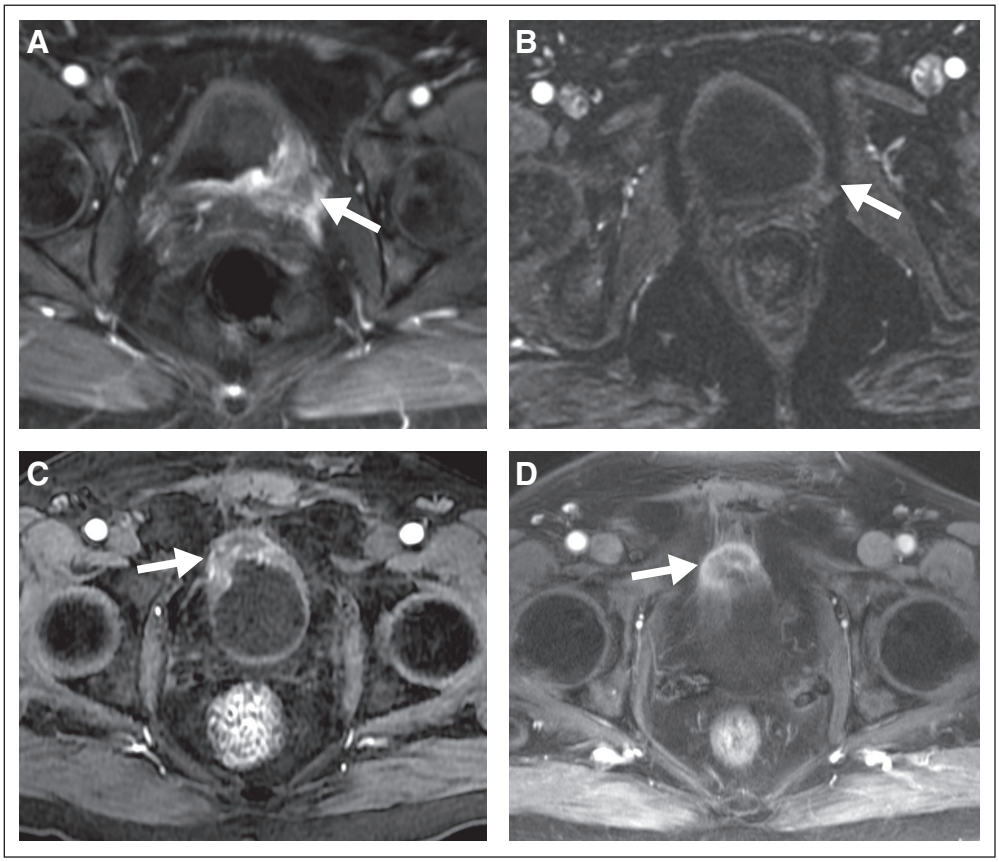

Fig 1. Gadolinium-enhanced magnetic resonance imaging (MRI) of radiologic (A, B) responder versus (C, D) nonresponder. (A, B) Significant adiologic response (RaR) after neoadjuvant dose-dense treatment in 49-year-old woman with muscle-invasive urothelial cancer (MIUC). T1W, fat-suppressed, gadolinium-enhanced MRI (A) at baseline and (B) after neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) demonstrated resolution of tumor bulk, thickness, and enhancement of left posterolateral bladder wall (arrow) at left ureterovesical junction, with no residual wall thickening or enhancement after treatment (arrow). At time of cystectomy, complete pathologic response was observed. (C, D) Absent RaR after neoadjuvant dose-dense treatment in 67-year-old man with MIUC and no RaR to therapy. T1W, fat-suppressed, gadolinium-enhanced MRI (A) at baseline and (B) after neoadjuvant ddMVAC demonstrated persistence of tumor bulk, thickness, and enhancement involving anterior bladder wall (arrows), with stranding extending into anterior perivesical fat. At time of cystectomy, tumor had invaded perivesicular tissue microscopically (stage ypT3aN0 disease).

DISCUSSION

This phase II multicenter study demonstrated a 49% pathologic downstaging to ≤ T1 in patients with MIUC, thus demonstrating ddMVAC is an effective alternative therapy to the MVAC regimen. All but two patients completed four cycles of chemotherapy as planned. The absence of febrile neutropenia and treatment-related deaths, along with the overall low rate of high-grade toxicity compared with MVAC, shows the tolerability of ddMVAC with pegfilgrastim support in the neoadjuvant setting. Extrapolating from the metastatic setting, the combination of gemcitabine and cisplatin (GC) has been

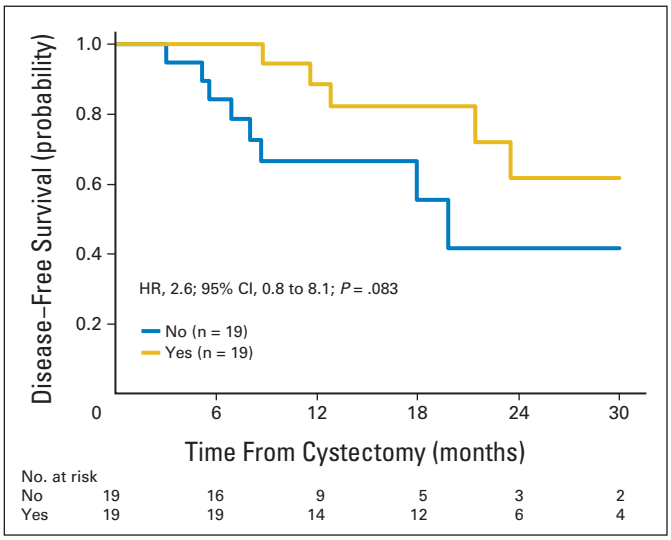

Fig 2. Association between disease-free survival and pathologic response. HR, hazard ratio.

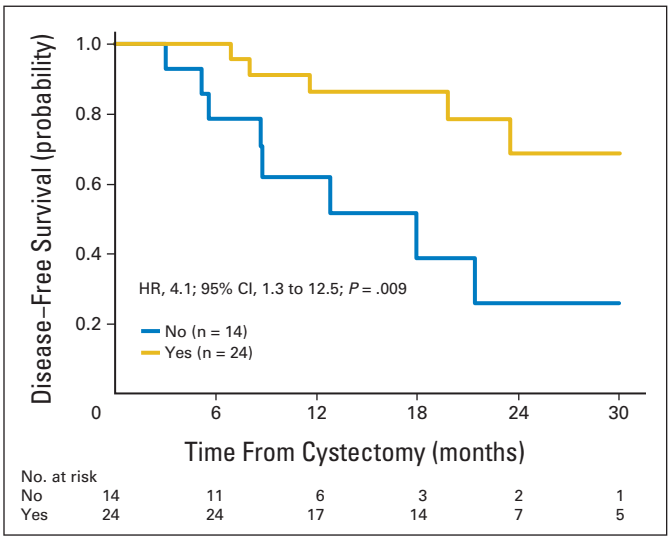

Fig 3. Association between disease-free survival and radiologic response. HR, hazard ratio.

commonly used as neoadjuvant therapy in clinical practice. The evidence for this practice is mostly based on retrospective studies, with mixed data regarding the efficacy of this regimen compared with MVAC. Some studies have suggested that GC is as effective as MVAC in the neoadjuvant setting, and one small prospective study from Brazil showed four of 15 patients achieved pT0 at cystectomy with three cycles of neoadjuvant GC.[14] Meanwhile, another study showed little pathologic downstaging with GC and suggested that MVAC should remain the standard treatment for MIUC.[13]

Recently, two similar phase II studies of neoadjuvant ddMVAC in MIUC were reported in abstract format. The first study showed a 48% rate of PaR to ≤ pT1 disease in 40 patients who underwent three cycles of ddMVAC.[15] In this study, only 7% of patients had lymph node positivity on imaging. The second study excluded patients with positive lymph nodes and added bevacizumab to four cycles of ddMVAC. This study showed a 53% rate of PaR to ≤ pT1 disease.[16] In contrast to these two studies, our study included a significant proportion of patients (43%) with low-volume lymph node disease (cN1) on imaging, providing us with the opportunity to examine the potential efficacy of ddMVAC in these patients. Overall, 14 (82%) of 17 patients with clinical N1 disease were pathologic N0 at the time of surgery, suggesting ddMVAC is able to sterilize small-volume lymph node disease. One limitation is that patients with cN1 disease were not sampled before chemotherapy; thus, the possibility of false-positive lymph nodes on imaging cannot be fully excluded.

Furthermore, our study is the first prospective trial to our knowledge to examine the association between PaR, RaR, ERCC1 expression, serum tumor markers, and DFS in patients with MIUC receiving ddMVAC neoadjuvant chemotherapy. The subgroup analysis showed both PaR and RaR were associated with DFS, although this trend did not meet statistical significance.

Additionally, we hypothesize that RaR could also be of great utility in the clinical management of MIUC, where the lack of RaR denoted refractory disease, indicating the need for more aggressive subsequent treatment approaches, such as additional or alternative chemotherapy as well as extensive lymph node dissection. RaR and PaR in this study provide complementary information. Specifically, RaR in primary bladder tumors is defined by a > 50% decrease in the product of longest diameters and delayed enhancement of residual tumor, and there is no specific T stage that must be achieved for RaR to be present. The purpose of the RaR definition is to enhance the prognostic information that can be offered to a patient; histologic examination remains the gold standard in determining a patient's final stage. The overall degree of change in bladder tumor burden in response to chemotherapy is easily demonstrated by MRI, and RaR as defined in this report also correlates with DFS. Pathologic T stage at surgery and the overall change in the primary tumor as demonstrated on post-treatment imaging are separate but important prognostic indicators. However, the criteria used to define RaR with contrast-enhanced imaging will need to be prospectively validated in patients with MIUC receiving neoadjuvant chemotherapy.

Initially, the role of ERCC1 as a predictor of platinum sensitivity was highlighted in a large study of patients with completely resected non–small-cell lung cancer, where ERCC1-negative tumors seemed to benefit from cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumors did not.[11] In bladder cancer, a retrospective study demonstrated that patients expressing low levels of ERCC1 mRNA exhibited a significantly higher median survival as well as a trend toward longer time to disease progression, suggesting that this marker may also hold promise in urothelial cancer.[17] Our ERCC1 analysis, which was exploratory given the limited power for anything but large effects, could not detect a statistically significant association with PaR or DFS. It is important to note that at the time of our data analysis, an update from the initial lung cancer study revealed none of the 16 commercially available antibodies against ERCC1 could distinguish among the functional versus nonfunctional ERCC1 protein isoforms, suggesting that at this time, ERCC1 IHC has limited utility in predicting cisplatin sensitivity.[18]

Monitoring serum tumor markers (CA19-9, CA125, or beta-HCG) has been suggested as an assessment for chemotherapy response in patients with advanced bladder cancer.[19,20] However, unlike in metastatic disease, few patients with MIUC had elevated tumor markers, and there was no association between postchemotherapy tumor marker normalization and response.

Further refinement of neoadjuvant chemotherapy in MIUC will include several key avenues of research. Further optimization of dosing schedules and rational drug combinations are both needed. Discovery and validation of biomarkers indicative of chemotherapy sensitivity permit the matching of appropriate therapies with suitable patients for improved treatment outcome. In keeping with these ideas, two ongoing trials (NCT01611662 and NCT01589094) are examining the outcome of neoadjuvant dose-dense GC in patients with MIUC. Combining chemotherapy with antiangiogenesis agents has also been examined. However, the addition of vascular endothelial growth factor receptor inhibitor sunitinib to traditional neoadjuvant chemotherapy with GC has shown excessive toxicity.[21] A new model for identifying biomarkers—the coexpression extrapolation algorithm (ie, COXEN model)—is currently being studied in a cooperative group trial.

In conclusion, ddMVAC neoadjuvant chemotherapy with growth factor support was well tolerated and safe and resulted in favorable pathologic and radiologic outcomes. The DFS analysis demonstrated a strong and clinically meaningful association with PaR and RaR. However, determining the real effect of neoadjuvant ddMVAC on DFS and OS will require longer follow-up and a phase III randomized study in the neoadjuvant setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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REFERENCES

1. Grossman HB, Natale RB, Tangen CM, et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349:859-866, 2003
2. Griffiths G, Hall R, Sylvester R, et al: International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. J Clin Oncol 29:2171-2177, 2011
3. Advanced bladder cancer overview collaboration: Neoadjuvant chemotherapy for invasive bladder cancer. Cochrane Database Syst Rev 2:CD005246, 2005
4. Sternberg CN, Yagoda A, Scher HI, et al: Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium: Efficacy and patterns of response and relapse. Cancer 64:2448-2458, 1989
5. Loehrer PJ Sr, Einhorn LH, Elson PJ, et al: A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: A cooperative group study. J Clin Oncol 10:1066-1073, 1992
6. Sonpavde G, Goldman BH, Speights VO, et al: Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. Cancer 115:4104-4109, 2009
7. Sternberg CN, de Mulder PH, Schornagel JH, et al: Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organisation for Research and Treatment of Cancer Protocol No. 30924. J Clin Oncol 19:2638-2646, 2001
8. The World Medical Association (WMA): The WMA declaration of Helsinki 1960 with recommendations on biomedical research on human subjects (modified in 1975, 1980 and 1989) [in Romanian]. Chirurgia (Bucur) 93(2):138-140, 1998
9. Schrier BP, Peters M, Barentz JO, et al: Evaluation of chemotherapy with magnetic resonance imaging in patients with regionally metastatic or unresectable bladder cancer. Eur Urol 49:698-703, 2006
10. Barentsz JO, Berger-Hartog O, Witjes JA, et al: Evaluation of chemotherapy in advanced urinary bladder cancer with fast dynamic contrast-enhanced MR imaging. Radiology 207:791-797, 1998
11. Olaussen KA, Dunant A, Fouret P, et al: DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 355:983-991, 2006
12. Atkinson EN, Brown BW: Confidence limits for probability of response in multistage phase II clinical trials. Biometrics 41:741-744, 1985
13. Weight CJ, Garcia JA, Hansel DE, et al: Lack of pathologic down-staging with neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder: A contemporary series. Cancer 115:792-799, 2009
14. Herchenhorn D, Dienstmann R, Peixoto FA, et al: Phase II trial of neoadjuvant gemcitabine and cisplatin in patients with resectable bladder carcinoma. Int Braz J Urol 33:630-638, 2007
15. Plimack ER, Hoffman-Censits JH, Viterbo R, et al: Neoadjuvant accelerated MVAC (AMVAC) in patients with muscle invasive bladder cancer: Results of a multicenter phase II study. J Clin Oncol 30:283s, 2012 (suppl; abstr 4526)
16. Siefker-Radtke AO, Kamat AM, Corn PG, et al: Neoadjuvant chemotherapy with DD-MVAC and bevacizumab in high-risk urothelial cancer: Results from a phase II trial at the MD Anderson Cancer Center. J Clin Oncol 30:282s, 2012 (suppl; abstr 4523)
17. Bellmunt J, Paz-Ares L, Cuello M, et al: Gene expression of ERCC1 as a novel prognostic marker in advanced bladder cancer patients receiving cisplatin-based chemotherapy. Ann Oncol 18:522-528, 2007
18. Friboulet L, Olaussen KA, Pignon JP, et al: ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. N Engl J Med 368:1101-1110, 2013
19. Cook AM, Huddart RA, Jay G, et al: The utility of tumour markers in assessing the response to chemotherapy in advanced bladder cancer. Br J Cancer 82:1952-1957, 2000
20. Dexeus F, Logothetis C, Hossan E, et al: Carcinoembryonic antigen and beta-human chorionic gonadotropin as serum markers for advanced urothelial malignancies. J Urol 136:403-407, 1986
21. Galsky MD, Hahn NM, Powles T, et al: Gemcitabine, cisplatin, and sunitinib for metastatic urothelial carcinoma and as preoperative therapy for muscle-invasive bladder cancer. Clin Genitourin Cancer 11:175-181, 2013

GLOSSARY TERMS

Biomarker: A functional biochemical or molecular indicator of a biologic or disease process that has predictive, diagnostic, and/or prognostic utility.

Disease-free survival: The survival period spanning the time from surgery to a recurrence of cancer.

Neutropenic fever: An oral temperature of at least 100.4°F for at least 1 hour when the absolute neutrophil count is $< 0.5 \times 10^9$/L.

Pathologic complete response: The absence of any residual tumor cells in a histologic evaluation of a tumor specimen.

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